Thiouracil in Thyroid Diseases*

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SINCE Plummer,[10] in 1923, introduced the use of iodine for preoperative preparation of patients in the treatment of hyperthyroidism, other methods of subtotally destroying the hyperplastic thyroid tissue have been employed less frequently and enthusiastically. Renewed attention has been paid to radiation therapy since the discovery of radioactive isotopes of iodine. Lately, pharmacologic studies on chemotherapeutic agents, the sulfonamides, have attracted the attention of many groups of workers in the field of thyroid disease, in the hope of finding chemical agents for the medical treatment of hyperthyroidism.

Mackenzie, Mackenzie and McCollum,[7] Richter and Clisby,[12] Kennedy[5] and Astwood and his associates[1] showed that sulfonamides and derivatives of thiourea inhibit the formation of thyroid hormone. Since publication of this work, many reports indicate that thiouracil is the most successful agent of the chemical compounds investigated, although propyl derivatives may be equally effective and less toxic.[2] There is now no doubt that thiouracil, in proper dosage, will inhibit formation of thyroid hormone in patients with toxic goiter and cause a remission in the symptoms of this disease as long as the drug is administered.

From the clinical standpoint, certain questions must be answered before thiouracil can be evaluated in the therapy of hyperthyroidism. In the preparation of patients for thyroidectomy, is thiouracil more efficient and safer than iodine? Does it take longer with thiouracil than with iodine to produce a remission? Are there greater dangers from toxic effects of thiouracil? Can this drug alone, without using methods for destruction of the thyroid gland, permanently inhibit the excess production of thyroid hormone? Is thiouracil effective only during the period of its administration?

PHARMACOLOGY OF THIOURACIL

The pharmacology of thiouracil has been best summarized by Williams, Kay and Jandorf.[14] Thiouracil is rapidly absorbed from the gastro-intestinal tract, an appreciable concentration being found in the blood within 30 minutes after administration. With divided daily doses totaling 0.2 to 1.2 grams, concentration in the blood varies from 0.8 to 6.4 mg. per cent. Most of the drug is in the cells in the blood stream. Excretion through the kidneys is rapid. Thiouracil is distributed through all tissues of the body and, according to Williams and his associates, is sometimes found in large quantities in bone marrow, thyroid, ovaries and pituitary while relatively small concentrations are found in striated muscle, testes and liver. These workers noted also that adenomata of the thyroid gland have a higher concentration of thiouracil than does normal thyroid tissue. Cerebrospinal, pericardial and edema fluids contain less thiouracil than whole blood; concentration in pleural and ascitic fluid is about that of blood and concentration in milk is three times that of blood. The drug is destroyed rapidly in the stomach and by contents of the small intestine. It is also destroyed by certain tissues of the body.

The exact mechanism of action of thiouracil on the thyroid is not known. The action is a direct one on this gland with suppression of hormone production. It has been postulated that the enzyme diiodotyrosinase is inhibited so that diiodotyrosine is not converted to thyroxin. Harington and Rivers[4] have shown recently that conversion of diiodotyrosin to thyroxin is almost entirely suppressed in vitro by sodium thiosulphate.

DOSAGE

In preoperative use of thiouracil, the best dosage seems to be between 0.8 and 1.0 gm. given in evenly divided dosages of 0.2 gm. each throughout the waking hours during the first two to three weeks. If the patient is not then ready for surgery, the dose should be decreased to a total of 0.6 gm. per day and at the end of another two weeks to 0.4 gm. per day. None of the patients under my observation has needed over 33 days of preparation for surgery, so a dose as low as 0.4 gm. has been given only experimentally. My experience has been that patients respond much better with 0.8 to 1.0 gm. daily than with small doses. With nonsurgical treatment of hyperthyroidism, the maintenance dose is 0.2 gm. daily to 0.1 gm. every other day.

Two recent reports[8,13] have presented the toxic effects in large series of patients. In one series of 1,091 patients, it was stressed that there is one potentially fatal complication of the drug, agranulocytosis, which was responsible for the five deaths that could be attributed to thiouracil. It should be emphasized that this fatality rate of one half per cent is approximately the same as the surgical mortality in recent years in clinics having a wide experience in thyroid diseases. Moore and his associates[9] have pointed out that 27 of 781 patients, or 3.4 per cent, developed a leukopenia (of 3,000 white blood cells or less) and that 19 of 1,091 patients, or 1.74 per cent, developed agranulocytosis. One fourth of all patients in this series with agranulocytosis died. Chart I shows the response of one patient to thiouracil. The first bout of fever, leukopenia and cervical lymphadenopathy ended after the drug was discontinued and penicillin was administered, but a recrudescence occurred coincident with a streptococcal wound infection some two and a half weeks later. Patients who have had

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* Read before the Section on General Medicine at the Seventy-fifth Annual Session of the California Medical Association, Los Angeles, May 7-10, 1946.

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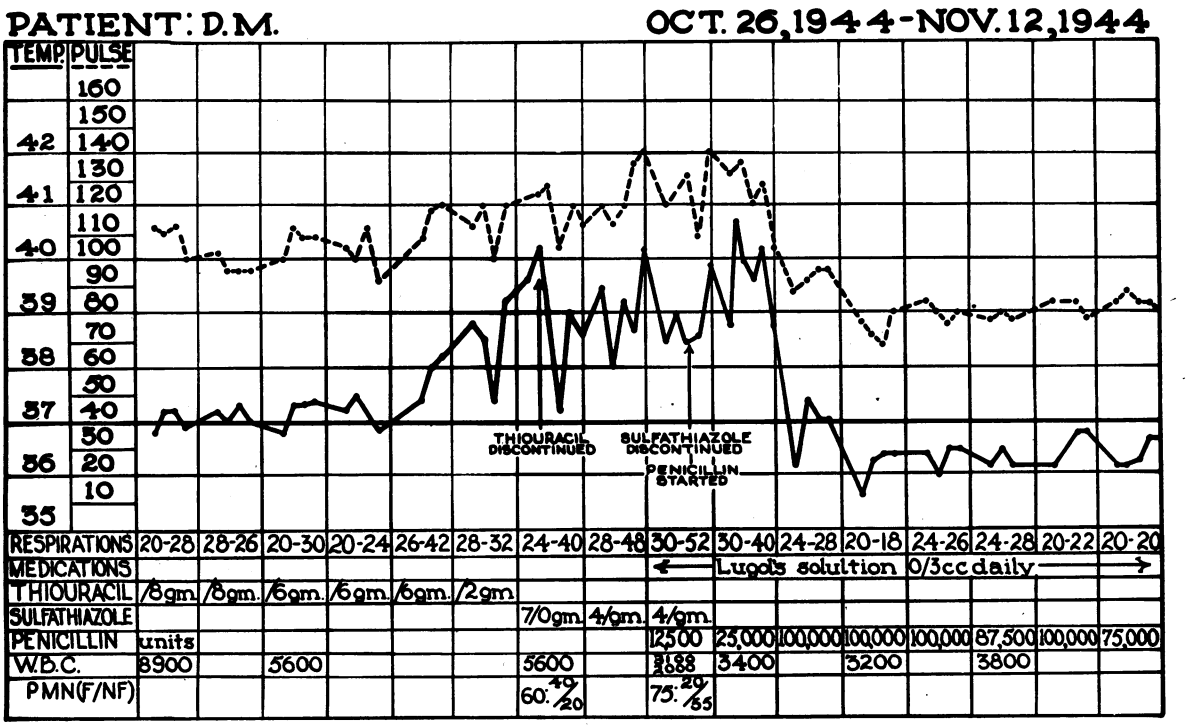
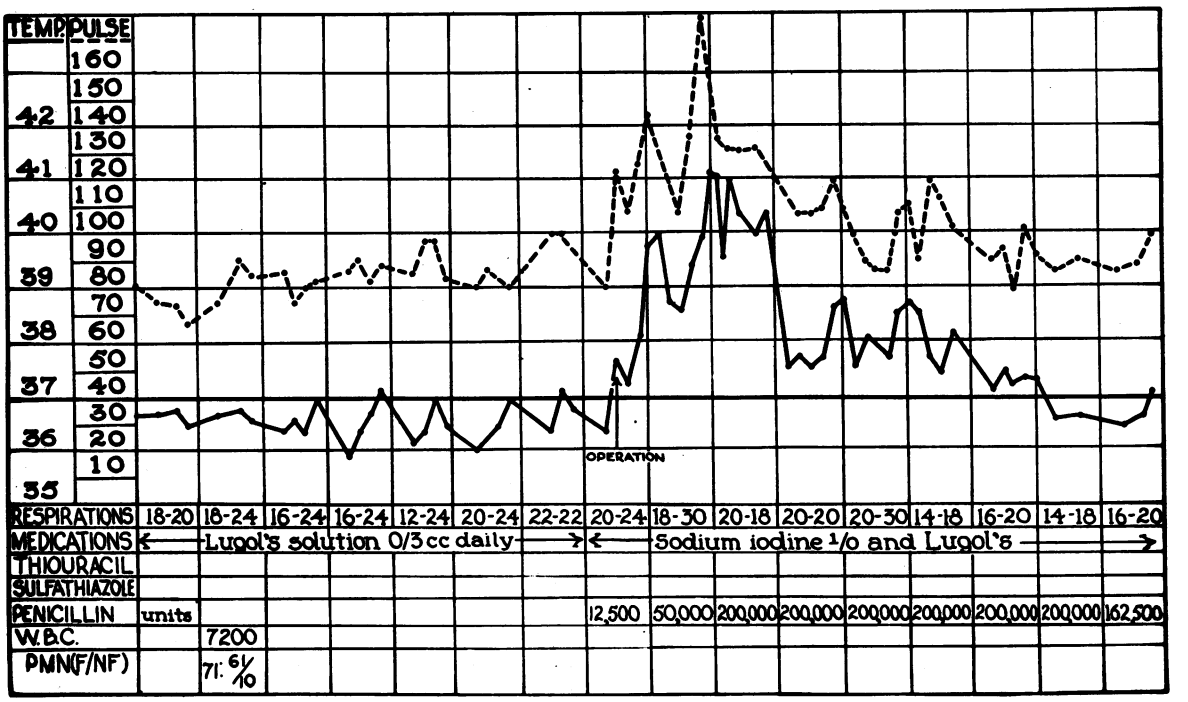
suppression of the function of the bone marrow are candidates for further such difficulties if any infection supervenes, even weeks after the original cause of the suppression has been removed. Leukopenia usually appears between the fourth and eighth week but it has been noted as early as the fifth day and as late as the fifth month during thiouracil therapy. To prevent any serious complications, a white blood cell count should be done repeatedly, preferably at least every third day, and

CHART I

THIOURACIL TOXICITY (FEVER AND LEUKOPENIA)





every day, if a trend toward leukopenia is noted. Intervals of three weeks or longer between counts should not be condoned.

Drug fever (Chart II) occurs in about 5 per cent of patients on thiouracil, and does not always indicate that the drug must be discontinued, although the experience at the University of California has suggested that most such patients no longer can tolerate this drug. About 5 per cent of patients have enlargement of lymph nodes and some of the salivary glands. Nausea and vomiting are encountered occasionally. Edema and myxedema have been reported. Skin rashes similar to those seen with sulfonamides are common. Hepatic damage has been noted.

The experience at the University of California Hospital has been that the postoperative course of really sick thyrotoxic patients has been smoother, with less fever and tachycardia, when these patients have received thiouracil preoperatively. On the other hand, when 3 to 5 grams of thyroid tissue are left *in situ* as is our custom in patients prepared in the usual manner with iodine, a much higher percentage have developed hypothyroidism even though thiouracil is discontinued within one to five days postoperatively. In fact, a third of our patients become hypothyroid, a figure that is about twice that of patients receiving iodine alone.

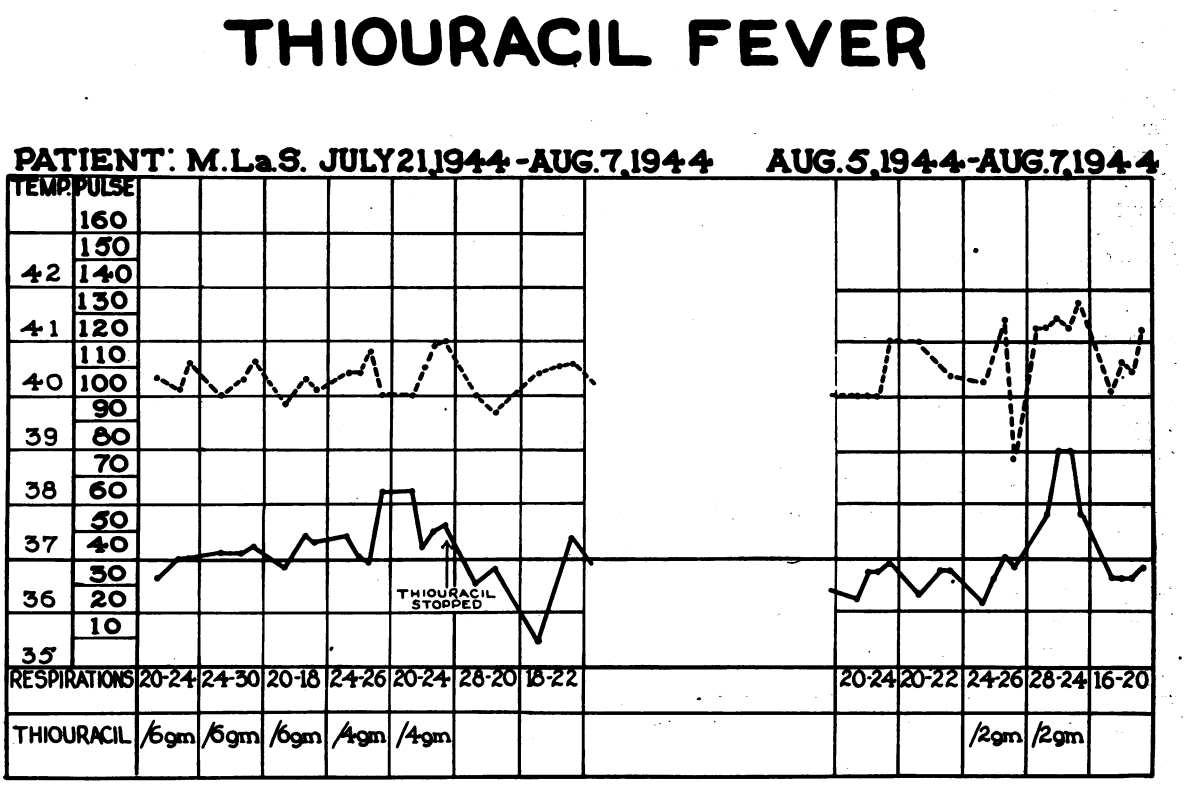
Only one of 41 patients in whom serial measurements of exophthalmos were made pre- and postoperatively showed a significant progression of exophthalmos. However, the patient with severer grades of exophthalmos is still not a candidate for thiouracil in spite of these reassuring figures since, according to the work of others, progression of exophthalmos has occurred during treatment with thiouracil.

PREOPERATIVE PREPARATION OF PATIENTS WITH THIOURACIL

Iodine produces a remission in Graves' disease by causing storage of thyroid hormone within the gland. The subsequent fall in basal metabolic rate and the clinical improvement that follows depend on the destruction and excretion of the excess thyroid hormone in the body; thus the rate of fall of the metabolism is similar to that of a patient following thyroidectomy, or to that of a patient with myxedema when thyroid therapy is stopped. If the administration of iodine—which, histologically, causes involution of the hyperplastic tissue—fails to produce this usual rate of fall in basal metabolism, it indicates, at least theoretically, that it has not been totally effective in damming thyroid hormone in the thyroid gland.

Thiouracil, by inhibition of hormone production, causes a fall in metabolic rate similar to that seen with iodine.[11,12] However, the thyroid gland, instead of involuting, becomes more hyperplastic. The delayed response in patients who have received iodine prior to thiouracil probably is due to the release of previously stored hormone. This means that the body must not only destroy and excrete the excess of thyroid hormone in its tissues but also that released from the thyroid gland with a consequently slower fall in the basal metabolic rate and slower amelioration of the clinical symptoms of hyperthyroidism. It should be mentioned that although half of our patients had been treated with iodine within a month prior to the use of thiour-

CHART II



acil, the average time between the start of therapy and operation under our care was only two days longer than in patients who had received no iodine.

Technical problems in surgical procedure arise because of the increased friability and vascularity of the thyroid gland of patients treated with thiouracil. Tissues are harder to handle and bleeding is more difficult to control. As one surgeon, H. Glenn Bell, phrased it: "Clamping a thiouracil-treated thyroid is like trying to put a clamp in a bowl of cornmeal mush." These technical problems can be avoided by the addition of iodine for one to two weeks prior to subtotal thyroidectomy.

At the University of California Hospital, we have not felt that thiouracil offers any advantages over iodine for the average patient with either a toxic diffuse or toxic nodular goiter. However, very sick patients with coincident ectopic rhythms and cardiac failure or very toxic patients who are in a severe exacerbation of hyperthyroidism and perhaps poorly controlled by iodine are excellent candidates for this drug. Of course, repeated leukocyte counts should be made and toxic effects should be watched for during preoperative preparation. All the other medical measures also should be used just as they are when iodine is given preoperatively. If thiouracil did not present the risk of serious toxic effects, it could be used in all cases rather than in selected groups.

Astwood[13] and many others have used thiouracil in the medical treatment of hyperthyroidism. There is no doubt from reports to date that a remission of symptoms will occur and can be maintained as long as small doses, such as 0.1 to 0.2 gm. daily, are given. The percentage of individuals in whom symptoms of hyperthyroidism recur when thiouracil is discontinued varies widely. Van Winkle and associates[10] report a minimum recurrence of 33.7 per cent, a figure that will almost certainly increase as hyperthyroid patients are observed for longer periods after thiouracil has been discontinued. No reports have stated specifically that thyroid glands return to normal size and consistency, which should also make one skeptical about "cures." The facts just stated, plus the expense of laboratory work and lack of evidence that hyperfunctioning thyroid tissue is permanently suppressed, suggest that thiouracil, as a single therapeutic agent in hyperthyroidism, will not long be used by experienced clinicians. This statement, however, does not apply to newer derivatives now being used experimentally.

King and Rosellini[14] have reported some success in thyroiditis from thiouracil. Thyroiditis which is subacute and not infectious in the sense that bacteria can be cultured from surgical speciments, responds to this drug. In such cases the patients have an enlarged, tender, firm, and spontaneously painful thyroid with local pressure symptoms, often fever, and an elevated sedimentation rate. There may be symptoms of hyperthroidism but usually only general irritability and lack of well-being. King and Rosellini state that thiouracil in doses of 0.2 gm. daily shortened the course of the disease in most of their patients. At the University of California Hospital, five of seven such patients seemed to respond favorably to thiouracil. An eighth patient, who did not respond at all, proved to have multiple hemorrhages in multiple nodules. Our experience indicates that dosage levels of 0.6 to 0.8 gm. per day may be more effective than the original dose of 0.2 gm., and that thiouracil must be continued for two to three weeks or longer.

SUMMARY

Thiouracil is a useful drug in preparation of thyrotoxic patients for surgical intervention when the hyperthyroidism is severe and complicated. It has not been proved better than iodine in moderate hyperthyroidism when used preoperatively. Thiouracil has not consistently produced a permanent remission in hyperthyroidism after the drug has been withdrawn. Nonbacterial (subacute) thyroiditis may respond to thiouracil therapy, although the reasons for this are far from clear. The most dangerous result of the toxic effect of thiouracil is agranulocytosis.

Grateful acknowledgment is made to the Lederle Company for the Deracil (thiouracil) used in our studies.

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